Articles

AIDS-Related Disseminated Histoplasmosis in San Francisco, California

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The published reports of patients with the acquired immunodeficiency syndrome (AIDS) with disseminated histoplasmosis come mostly from institutions located in endemic areas for histoplasmosis, where disease is thought to occur by either primary infection or reactivation. The characteristics of reactivation disease are not well delineated. We describe the clinical features of reactivation disseminated histoplasmosis in 46 residents of San Francisco, California, with AIDS who did not report recent travel to an area endemic for histoplasmosis. Patients presented with illness lasting days to months, manifested most frequently by fever, chills, sweats, cough or dyspnea, gastrointestinal complaints, malaise, and weight loss. Physical examination and imaging studies were notable for hepatosplenomegaly, lymphadenopathy, or abnormal pulmonary findings in more than half of patients. Laboratory studies revealed a high rate of cytopenia, elevated serum lactate dehydrogenase levels, abnormal liver function test values, respiratory alkalosis with hypoxemia, and a median CD4 lymphocyte count of 36 × 10^9 per liter. The clinical presentation of reactivation disseminated histoplasmosis in patients with AIDS living in San Francisco is similar to that of disseminated histoplasmosis reported in patients with AIDS living in endemic areas. Reactivation disseminated histoplasmosis should be considered in any AIDS patient with a low CD4 lymphocyte count, a febrile illness, and a history of travel or residence in an endemic area.

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The fungus *Histoplasma capsulatum* is endemic in the central United States and in areas of Latin America, the Caribbean, Africa, and Southeast Asia, with cases of disease reported from all continents.[1] The hyperendemic area in the United States includes the Mississippi and Ohio river valleys and extends south into Louisiana and the Gulf Coast. Patients with the acquired immunodeficiency syndrome (AIDS) with active *H capsulatum* infection tend to present with a severe illness marked by dissemination. Urban centers within the hyperendemic area such as Indianapolis, Indiana, and Kansas City, Missouri, have reported an incidence of histoplasmosis in patients with AIDS as high as 26%.[2] Several reports have described the clinical features of disseminated histoplasmosis in AIDS patients from endemic areas.[2–4] These cases may represent a mixture of two patient populations. The first group of patients are those in whom an acute pulmonary infection with *H capsulatum* develops that is not contained, leading to early dissemination. The second group consists of those in whom latent *H capsulatum* infection reactivates from a previous infection and subsequently disseminates, in a manner reminiscent of reactivated tuberculosis. The relative importance of each mechanism of dissemination has been debated but is not known.[5,6] Even a prospective study of histoplasmosis in patients infected with the human immunodeficiency virus (HIV) living in the endemic area of Kansas City was not able to determine the contribution of these two mechanisms, probably because of the high rate of skin test anergy and aberrant serologic responses in these patients.[3,2] It is also not clear whether reactivation histoplasmosis presents in the same manner as acute disseminated disease in patients with AIDS. By analyzing the clinical characteristics of a large group of AIDS patients diagnosed with disseminated histoplasmosis while liv-

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ABBREVIATIONS USED IN TEXT
AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
HPA = *H capsulatum* polysaccharide antigen

ing in a nonendemic area (California) and without recent acute exposure, we sought to study reactivation disease in isolation.

Patients and Methods

Patients with disseminated histoplasmosis and AIDS were identified through a review of medical record discharge diagnoses and microbiology culture logs from San Francisco General Hospital Medical Center and Moffitt-Long Hospital in San Francisco, California, between 1981 and 1994. Disseminated histoplasmosis was defined by the presence of extrapulmonary *H capsulatum* detected by culture, peripheral blood smear, or histopathologic examination in association with an acute illness. Reactivation disease was defined as disease in a San Francisco resident who did not report travel within the previous three months to an endemic area. Because the incubation period for acute histoplasmosis may be as long as three weeks, a three-month period without exposure to the fungus was chosen to exclude patients who might have acute disease with subsequent dissemination. None of the patients in this study with documented disseminated histoplasmosis had symptoms for longer than three months. Criteria outlined by the Centers for Disease Control and Prevention were used to define AIDS.[7] All cases were studied retrospectively. Data were extracted from medical records using a case record form and entered into a database (Paradox) for analysis.

Results

Patient Characteristics

A total of 76 patients were initially identified as having histoplasmosis by discharge diagnosis or culture. Of these, 13 were excluded because they were HIV-negative and 7 because of incomplete or absent medical records. Two patients were excluded because the diagnosis of histoplasmosis could not be confirmed. Of the 54 remaining cases, 8 were excluded because they were not San Francisco residents or were documented to have traveled within three months of illness to an area endemic for histoplasmosis, leaving 46 patients with AIDS for the evaluation of disseminated histoplasmosis.

The median age of the 46 patients studied was 36 years (range, 21 to 60), and 45 patients were male (98%). The racial composition of the group consisted of 21 white non-Hispanic (46%), 18 Hispanic (39%), 4 African-American (9%), and 3 Asian (6%) patients. Previous opportunistic infections or malignant neoplasms were noted in 42 patients (91%). Active opportunistic coinfections were present at the time of diagnosis in 25 patients (54%) (Table 1).

Table 1.—*Active Coinfections Present at Diagnosis of Disseminated Histoplasmosis*

Infection	*Patients Infected (n = 46), No. (%)*
Cytomegalovirus	9 (20)
Mycobacterium avium	8 (17)
Pneumocystis carinii pneumonia	7 (15)
Intestinal parasites	7 (15)
Bacteremia	5 (11)
Herpes simplex virus	5 (11)
Kaposi's sarcoma	4 (9)
Candidiasis	2 (4)

A documented travel history to an area endemic for histoplasmosis was obtained in 40 of 46 patients (87%). Of the 40 cases with known exposure, 34 patients were born in an endemic area (85%) and 6 patients were born outside of but traveled through endemic areas (15%). Of the 40 patients, 21 (53%) were exposed in the United States, 15 (38%) in Latin America or the Caribbean, 3 (8%) in both areas, and 1 (3%) in Asia. The time interval since last known travel to an endemic area was documented in 23 cases. The median time to last exposure was two years (range, 0.25 to 23 years).

Clinical Presentation

Patients' chief complaints, by order of frequency, were fever, cough, shortness of breath, abdominal pain, skin or oral lesions, and diarrhea. Duration of the chief complaint varied between 2 and 90 days, with a median of 14 days. In the 46 patients studied, 43 had fever (93%), 33 noted chills or sweats (72%), 27 reported weakness or malaise (59%), and 22 had weight loss (48%). These symptoms tended to be subacute, lasting for weeks before diagnosis in most patients. Table 2 lists symptoms by the most frequently involved organ systems, as well as physical findings. Results are compared with studies of AIDS patients from the endemic areas of Indianapolis, Indiana, and Houston, Texas.[2,3]

Physical findings were notable for fever, with 39 (85%) patients having a temperature higher than 38.5°C (101.3°F) before treatment. The median maximum temperature recorded during the evaluation of illness in the days to weeks before treatment was 39.8°C (103.6°F), with a range of 36.9°C to 41.0°C (98.4°F to 105.8°F). Thirteen patients had a systolic blood pressure of less than 90 mm of mercury (28%). The median pulse was 100 beats per minute with a range of 72 to 140. The median respiratory rate was 20 breaths per minute with a range of 16 to 40. Organomegaly was listed if enlargement was noted on physical examination or radiographic or ultrasonographic imaging.

The results of laboratory tests are summarized in Table 3. Only 1 patient of the 46 had a hemogram at

Table 2.—*Symptoms and Physical Findings in the Study Patients Compared With Reports of Similar AIDS Patients From Endemic Areas*

	Present Study, n = 46 No. (%)	*Wheat et al., 1990[2], n = 72* No. (%)	*Johnson et al., 1988[3], n = 48* No. (%)
Symptoms by organ system			
Constitutional (fever)	43 (93)	69 (96)	39 (81)
Respiratory	31 (67)	38 (53)	10 (21)*
Gastrointestinal	30 (65)	2 (3)	9 (19)†
Nervous system	15 (33)	13 (18)	—
Integument	14 (35)	1 (1)	—
Physical findings			
Hepatomegaly	22 (48)	19 (26)	9 (19)
Splenomegaly	28 (61)	9 (12.5)	15 (31)
Lymphadenopathy	26 (57)	12 (17)	9 (19)
Skin lesions	14 (30)	1 (1)	>5 (>10)
Mucosal ulceration	10 (22)	—	—
Abnormal pulmonary	28 (61)	—	—
Abnormal CNS	7 (15)	—	—
Abdominal tenderness	16 (35)	—	—

CNS = central nervous system.
*Cough.
†Diarrhea.

diagnosis that was normal in all three cell lines. Pancytopenia was present in 21 patients (46%). At least one liver function test abnormality was present in 38 patients at diagnosis (83%). Eight patients had ferritin levels greater than 1,000 µg per liter (>1,000 ng per ml), and one patient had a level of 21,240 µg per liter (21,243 ng per ml). Arterial blood gas measurements revealed respiratory alkalosis in 24 of 28 patients tested (86%). Chest radiograph findings are described in Table 4.

Microbiology results are shown in Table 5. A total of 41 patients had blood specimens drawn for culture before therapy, with most patients getting multiple blood cultures, producing 132 specimens, of which 95 specimens eventually grew *H capsulatum*. Out of the 41 patients, 36 had at least one positive blood culture (88%). The median time between drawing a specimen for culture and its turning positive was 17 days, with a range of 6 to 52 days.

Pathology specimens were positive on histologic examination in 34 of 43 specimens, for a rate of 79% overall. Bone marrow biopsy was positive in 11 of 15 cases (73%), lymph node biopsy in 8 of 9 cases (89%),

Table 3.—*Laboratory Data for Study Patients at the Time of Diagnosis*

Test	*Normal Range*	*Median*	*Range*	*Patients With Abnormal Values, No.*	*Patients Tested, No.*
Hematocrit	39.8–52.2	29.8	17.5–45.0	43	46
Leukocyte count, × 10^9/liter	3.9–11.7	2.65	0.6–9.4	33	46
PMN, × 10^9/liter	1.7–8.0	1.9	0.5–7.7	18	43
Left shift	Absent			38	44
Platelets, × 10^9/liter	150–400	109	25–443	29	46
CD4 cells, × 10^9/liter	420–1,250	36	2–150	35	35
Bilirubin, mg/dl	0.1–1.2	0.55	0.1–5.5	6	46
AST, IU/liter	10–50	83	7–1,113	36	46
Alk Phos, IU/liter	30–115	183	43–1,730	34	45
LDH, IU/liter	110–220	509	164–5,760	35	38
PT, sec	<13.1	12.6	9.8–19.9	16	41
Creatinine, mg/dl	0.6–1.4	0.95	0.4–7.0	5	44
Arterial blood gases pH	7.35–7.45	7.45	7.15–7.64	12	28
Po_2, mmHg	80–100	72	32–100	22	28
Pco_2, mmHg	35–45	30	20–39	24	28

Alk Phos = alkaline phosphatase, AST = aspartate aminotransferase, LDH = lactate dehygrogenase, PMN = polymorphonuclear leukocytes, PT = prothrombin time.

Table 4.—*Chest Radiograph Findings in This Study Compared With 2 Studies From Areas Endemic for Histoplasmosis*

Finding	Present Study, n = 46 No. (%)	Wheat et al., 1990[2], n = 72 No. (%)	Sarosi and Johnson, 1992[4], n = 59 No. (%)
Normal	9 (20)	31 (43)	16 (27)
Abnormal	37 (80)	41 (57)	43 (73)
Diffuse infiltrate	27 (59)	32 (44)	34 (58)
Focal infiltrate	6 (13)	8 (11)	5 (8)
Lymphadenopathy	15 (33)	2 (3)	—
Calcified granuloma	7 (15)	2 (3)	2 (3)

skin biopsy in 5 of 5 cases (100%), bronchoalveolar lavage in 4 of 7 cases (57%), transbronchial biopsy in 2 of 2 cases, liver biopsy in 1 of 2 cases, and esophageal biopsy in 1 case. Hemoperitoneum developed in one patient who underwent liver biopsy, and the patient died. The median time from biopsy to pathology report was 2 days with a range of 1 to 15 days. A peripheral blood smear for intracytoplasmic yeast was positive in 9 of 13 cases (69%), with a turnaround time of 1 day or less.

Diagnosis

The initial or admitting diagnosis before microbiologic or pathologic confirmation was recorded for each patient. Common diagnoses were fever, pneumonia, pancytopenia, lymphadenopathy, and rule out *Pneumocystis carinii* pneumonia, Mycobacterium avium-complex bacteremia, tuberculosis, fungal infection, or lymphoma. Only 6 patients had fungal infection listed in the differential diagnosis, and just 1 of the 46 patients in this study had disseminated histoplasmosis specifically listed in the differential diagnosis of the presenting illness.

The diagnosis of disseminated histoplasmosis was not made in 4 patients, 2 of whom died before diagnosis and 2 of whom were lost to follow-up. In the 42 remaining patients, the method of first successful diagnosis was determined by establishing which diagnostic route led to identification of the disease and the initiation of treatment. Histoplasmosis was first diagnosed by histopathologic examination in 25 patients (60%), with the most frequent sites being bone marrow (7 patients), lymph node (6 patients), bronchoscopic biopsy or lavage (5 patients), and skin (3 patients). Culture for *H capsulatum* first revealed the diagnosis in 11 patients (26%), with blood the most frequent source, leading to a diagnosis in 9 patients. Review of the peripheral blood smear for intracytoplasmic yeast in leukocytes first revealed the diagnosis in 6 patients (14%).

Discussion

This retrospective case series of 46 patients represents the largest group of patients with AIDS and disseminated histoplasmosis from a nonendemic area reported to date,[8,9] although individual case reports have also described reactivation disseminated histoplasmosis in both patients with AIDS and those without AIDS.[10–13] Although histoplasmosis has been noted to occur in as many as 26% of AIDS patients from endemic areas, it has been suggested that the disease develops in less than 1% of AIDS patients from nonendemic areas.[5] The relatively low incidence of this opportunistic infection in AIDS patients residing in nonendemic areas may hamper its diagnosis, especially when other concurrent opportunistic infections are present (as occurred in half the cases we reviewed) that could explain clinical and laboratory abnormalities. In this study, physicians specifically listed histoplasmosis in their initial differential diagnosis of the presenting ill-

Table 5.—*Microbiology Results for* H capsulatum *Listed By Site Cultured*

Site Cultured	Present Study		Wheat et al., 1990[2]	
	Patients With Positive Culture, No.	Total Patients, No. (%)	Patients With Positive Culture, No.	Total Patients, No. (%)
Blood	36	41 (88)	32	35 (91)
Bone marrow	13	14 (93)	19	21 (90.5)
Respiratory	12	14 (86)	18	21 (86)
Lymph node	6	7 (86)	6	7 (86)
Urine	0	3 (0)	2	6 (33)
Cerebrospinal fluid	0	13 (0)	2	10 (20)
Liver	1	1 (—)	1	1 (—)
Skin	3	5 (60)	—	—

ness in only one patient. Greater awareness of this disease is needed in nonendemic areas such as the western United States.

Disseminated histoplasmosis is thought to occur by either primary infection, through the inhalation of exogenous fungal spores, or the reactivation of latent infection with previously acquired endogenous organisms. In nonendemic areas such as San Francisco, the lack of exogenous *H capsulatum* in the environment implicates the reactivation of latent infection as the source of disseminating organisms. Although histoplasmosis outbreaks have been documented in areas considered to be nonendemic such as Maryland[14] and central New York State,[15] these locations are relatively close to the endemic area, and *H capsulatum* was cultured from the outbreak sites, suggesting that microfoci of *H capsulatum* were responsible for the outbreaks.

In contrast, California is geographically isolated from the endemic area, and there are no published reports of histoplasmosis outbreaks or the detection of environmental *H capsulatum* from California using a Medline search from 1966 through 1996. The published cases of histoplasmosis from California have occurred in patients who have lived or traveled in endemic areas.[16,17] Although studies of histoplasmin skin test reactivity among large populations such as navy recruits demonstrate that positive histoplasmin skin tests can be found in people residing in California,[18] the data are most consistent with these tests representing cross-reactivity to *Coccidioides immitis*.[16,19,20] Because no microfocus of *H capsulatum* has been reported in California or the western United States, acute exposure with dissemination is highly unlikely.

Molecular evidence of reactivation disease in AIDS-associated disseminated histoplasmosis was presented by Keath and co-workers using restriction fragment length polymorphisms of *H capsulatum* nuclear and mitochondrial genes.[21] We think that this population of patients with AIDS living in California represents a relatively uniform collection of patients with reactivation histoplasmosis. Half of the patients were documented to have only a remote exposure to *H capsulatum*, and those patients known to have recently traveled to an endemic area were excluded from the study. All of the patients were residents of the San Francisco area. One patient had lived exclusively in San Francisco for 23 years after emigrating from El Salvador in Central America. There were no significant differences in clinical variables between the 23 patients with a chronologic travel history and the 23 patients without (data not shown). In their review of disseminated histoplasmosis in AIDS patients, Wheat and colleagues state, "Contrasted to tuberculosis, in which reactivation appears to be the common mechanism of infection in adults, reactivation appears to be infrequent in histoplasmosis."[2(p368)] Although this statement may be true in endemic areas, in nonendemic areas such as San Francisco, reactivation histoplasmosis is the only tenable explanation for most of the cases of disseminated histoplasmosis in AIDS.

A review of the clinical presentations in these 46 patients highlights the difficulty in making a diagnosis of disseminated histoplasmosis. Patients tended to present with nonspecific symptoms such as fever, chills, sweats, weakness, cough, or weight loss. These symptoms are compatible with many common afflictions in AIDS, including *M avium*-complex bacteremia, *P carinii* pneumonia, lymphoma, tuberculosis, and bacterial pneumonia. Symptoms were present for days to months before diagnosis. Physical examination findings or imaging studies frequently revealed hepatomegaly (48%), splenomegaly (61%), and lymphadenopathy (57%), consistent with the known predilection of *H capsulatum* for the reticuloendothelial system. These figures are similar to data derived from a study of abdominal computed tomographic findings in AIDS patients with disseminated histoplasmosis.[22]

Multiple laboratory abnormalities are usually present in AIDS patients with disseminated histoplasmosis, and these can provide a clue to the diagnosis. Only 1 patient of the 46 had a normal hemogram at diagnosis. We cannot exclude the possibility that the concurrent use of medications (such as zidovudine) may have contributed to these hematologic abnormalities, but the presence of cytopenia in patients receiving no medications argues that histoplasmosis alone may produce these effects. A leftward shift was noted on the examination of leukocytes in 86% of patients, although no patient had an elevated absolute leukocyte count. Although ferritin levels were measured in only a few patients in this study before treatment, we observed striking hyperferritinemia in several patients. Hyperferritinemia has been described before in AIDS-associated disseminated histoplasmosis, with one report of a patient with a ferritin level of 426,000 μg per liter.[23] Our experience with patients having disseminated histoplasmosis suggests that elevated ferritin levels rapidly fall with treatment and rise again with relapse.[24] Abnormal liver function test results were common, with at least one liver function test abnormality present in 83% of patients. Although lactate dehydrogenase levels were elevated in 92% of patients, the tissue source of this elevated enzyme is not known in these patients.

Pulmonary involvement in this disease is reflected in the high rate of abnormal chest radiographs and arterial blood gas analyses. Pulmonary involvement clearly does not distinguish between primary and reactivation histoplasmosis.

Microbiologic evaluation of these patients was usually successful but was not expedient. Although blood cultures were positive in 88% of patients, there was a substantial delay between drawing the specimen and obtaining a result. The median time to a positive blood culture was 17 days. One patient's blood culture did not turn positive until after 52 days of incubation. This delay explains why most patients were diagnosed by histopathologic examination despite having a high rate of positive cultures. A routine liquid media culture system was used in this study, which may require longer

incubation times and produce lower yields than obtained with a lysis-centrifugation system.[25,26] Another problem with standard blood cultures is that the specimens are routinely discarded after only five to seven days of incubation, which is insufficient time to grow *H capsulatum*. A high index of suspicion for histoplasmosis should lead health care professionals to obtain several blood specimens for culture, preferably lysis-centrifugation culture, with specific instructions for the laboratory to hold the culture for at least four weeks.

Histopathologic examination was also successfully used to make the diagnosis of histoplasmosis in a high percentage of patients, with 79% of specimens submitted being positive, but the time from test to result was much shorter than with culture. A median of two days elapsed between biopsy and pathology report, compared with 17 days for culture. The disadvantage of histopathology is the need for invasive procedures, but the advantage is the speed of diagnosis, which is paramount in acutely ill patients. Examination of the peripheral blood smear or buffy-coat preparation for identifying intracytoplasmic yeast in leukocytes is a cheap, rapid, noninvasive test with a yield of 69% in the 13 patients tested here and with a turnaround time of only one day. The disadvantage of the blood smear examination is that some experience is necessary for the correct identification of the yeast within leukocytes, and sensitivity of this test may be suboptimal.

Although no patient in this study had the initial diagnosis made by the *H capsulatum* polysaccharide antigen (HPA) test, HPA testing of blood and urine appears to be useful in diagnosing disseminated histoplasmosis in AIDS patients.[27,28] As for serologic tests, investigators have questioned the usefulness of serologic tests in AIDS patients with disseminated histoplasmosis.[5,29] There is no role for histoplasmin skin testing in the diagnosis of disseminated histoplasmosis.[30,31]

We suggest a diagnostic strategy for the evaluation of AIDS patients with suspected disseminated histoplasmosis based on both the yield and speed of each test. Early evaluation should include phlebotomy for blood cell counts and serum chemistry values (lactate dehydrogenase, ferritin, liver function tests), a peripheral blood smear for the detection of yeasts, and blood cultures (lysis-centrifugation). Abnormal laboratory test results help to drive further diagnostic evaluation, including invasive tests. The peripheral blood smear provides the opportunity for the immediate diagnosis and initiation of treatment, whereas the blood culture may provide a delayed diagnosis or may help confirm the diagnosis suggested by other means. Specimens for culture should be sent to the laboratory with specific instructions to incubate them for four to six weeks. In ill patients who require immediate intervention, further evaluation should include either tissue biopsy with histopathologic examination and culture or HPA testing of serum and urine. Bone marrow is a tissue that is relatively easy and safe to obtain, and it provides a good yield on both histologic examination and culture.

Although comparisons between this study of AIDS patients living in a nonendemic area and of those living in endemic areas are subject to numerous biases, some general conclusions are warranted. The clinical presentations of AIDS patients with disseminated histoplasmosis appear to be similar in both endemic and nonendemic areas. A notable exception was the higher incidence of lymphadenopathy noted on chest radiographs from patients in San Francisco (33%) compared with those in Indianapolis (3%).[2] This discrepancy may be due to institutional differences in radiologic interpretation, but the tenfold difference seems rather large for this alone.

In summary, disseminated histoplasmosis may occur as reactivation disease in patients with AIDS and should be considered in any AIDS patient with a low CD4 lymphocyte count, a febrile illness, and a history of travel or residence in an endemic area, even when other concurrent opportunistic infections are present. The clinical features of reactivation disseminated histoplasmosis in AIDS are similar to those found in AIDS patients residing in endemic areas. Multiple laboratory test abnormalities may help suggest the diagnosis. In patients who are critically ill with suspected disseminated histoplasmosis, rapid diagnosis by tissue biopsy or HPA testing of urine and serum should be undertaken, and early (empiric) initiation of antifungal therapy may be warranted.

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